REMARKS

The specification has been amended to reflect the 371 status. Claim 8 has been cancelled without prejudice corresponding to cancellation of 8 during prosecution of the international application. The multiple dependencies of the claims have also been removed to reduce the PTO filing fee.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached pages are captioned "**Version with markings to show changes made**".

Favorable action on the merits is solicited.

Respectfully submitted,

Fuminori SATO et al.

By [signature]
Warren M. Cheek, Jr.
Registration No. 33,367
Attorney for Applicants

WMC/dlk
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
August 15, 2001

DESCRIPTION

HETEROCYCLIC COMPOUNDS, INTERMEDIATES THEREOF AND ELASTASE INHIBITORS

This application is a 371 of PCT/JP00/01022 filed February 23, 2000.

TECHNICAL FIELD

The present invention relates to a novel heterocyclic compound being useful as a medicament, especially exhibiting a human neutrophilic elastase inhibitory activity, intermediates thereof, and a human neutrophilic elastase inhibitor containing as the active ingredient said heterocyclic compound.

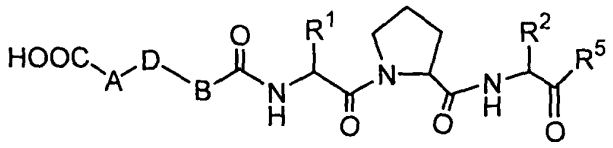
PRIOR ART

Human neutrophilic elastase (hereinafter, occasionally simply referred to as elastase) is a kind of serine proteases being massively released from the granules of neutrophile, which appear in the cases of infections or inflammatory diseases. Elastase is an enzyme hydrolyzing proteins such as elastin, collagen, proteoglycan, fibronectin, etc. which constitute the interstitum of intravital connective tissues such as lung, cartilage, vascular wall, skin, etc. In addition, it has been clarified that elastase acts on other proteins or cells as well.

In the living body, elastase keeps the homeostasis of the living body while the activities thereof are controlled by endogenous inhibitor proteins such as α_1-protease inhibitor, α_2-macrogloblin, secretory leukocyte protease inhibitor, etc. However, when a balance between elastase and the endogenous inhibitors is lost by the excessive release

or its ester, or a salt thereof.

2. The heterocyclic compound according to claim 1, which is a compound of the following formula (I-b):

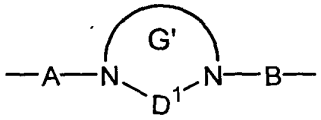


(I-b)

wherein A, B, D, R^1, R^2 and R^5 are as defined in claim 1,

or its ester, or a salt thereof.

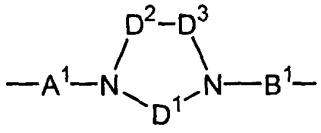
3. (amended) The heterocyclic compound according to claim 1 ~~or claim 2~~, wherein the group of the formula: -A-D-B- is a group of the following formula:



wherein A, B and D^1 are as defined in claim 1, Ring G' is a 5- to 9-membered, saturated or unsaturated heteromonocyclic group having 1 to 3 of other heteroatom selected from a nitrogen atom, an oxygen atom and/or a sulfur atom, and said heteromonocyclic group may have 1 to 3 substituents T^1 which are as defined in claim 1,

or its ester, or a salt thereof.

4. (amended) The heterocyclic compound according to claim 1 ~~or claim 2~~, wherein the group of the formula: -A-D-B- is a group of the following formula:

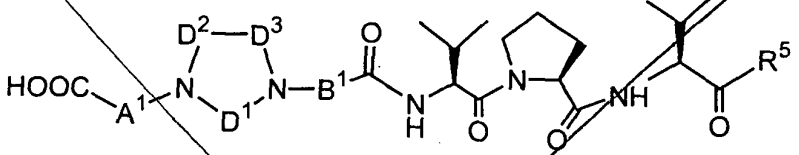


wherein A^1 is a methylene group or a group of the formula: $-CH_2CO-$, B^1

is a methylene group or a group of the formula: $-COCH_2-$, D^2 and D^3 are the same or different and each is a vinylene group being optionally substituted by a lower alkyl group, or a methylene group being optionally substituted by an oxo group or a lower alkyl group, D^1 is as defined in claim 1, provided that both D^2 and D^3 should not simultaneously be a vinylene group being optionally substituted by a lower alkyl group,

or its ester, or a salt thereof.

5. The heterocyclic compound according to claim 4, which is a compound of the following formula (I-c):



(I-c)

wherein D^1 and R^5 are as defined in claim 1, and A^1, B^1, D^2 and D^3 are the same as defined in claim 4,

or its ester, or a salt thereof.

6. The heterocyclic compound according to claim 5, which is selected from the following compounds, its ester, or a salt thereof:

Compound 1: 2-(3-carboxymethyl-2-oxo-1-imidazolidinyl)acetyl-L-valyl-N-[(1S)-3,3,3-trifluoro-1-isopropyl-2-oxopropyl]-L-prolinamide;

Compound 2: 2-(3-carboxymethyl-2,4-dioxo-1-pyrimidinyl)-acetyl-L-valyl-N-[(1S)-2-(2-benzoxazolyl)-1-isopropyl-2-oxoethyl]-L-prolinamide;

Compound 3: 2-(4-carboxymethyl-2,3-dioxo-1-piperazinyl)acetyl-L-valyl-N-[(1S)-2-(2-benzoxazolyl)-1-isopropyl-2-oxoethyl]-L-prolinamide;

Compound 4: 2-(3-carboxymethyl-2,4-dioxo-1-pyrimidinyl)-